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Nitrosamine, nitrate and nitrite in relation to gastric cancer: A case-control study in Marseille, France

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Abstract. A case-control study on gastric cancer and diet was conducted in Marseille (France). Ninety-two patients with histologically confirmed adenocarcinoma and 128 controls undergoing functional re-education for injuries or trauma were interviewed by a trained dietician using a dietary history questionnaire on their usual diet during the year preceding the first symptoms for cases, or preceding interview for controls. Intake of nitrite, nitrate and pre-formed N-nitrosodimethylamine (NDMA) from food was estimated using a food composition table compiled ad hoc. Odds ratios (ORs) were calculated after adjustment for age, sex, occupation and calorie intake. The results indicated that high intake of NDMA was associated with increased risk for gastric cancer. The ORs for the second and third tertile of NDMA intake were: $OR_2 = 4.13$ (95% CI = 0.93 to 18.27) and $OR_3 = 7.00$ (95% CI = 1.85 to 26.46). Intake of nitrate and nitrite was not associated with increased risk of stomach cancer. Consumption of vegetables was protective in general and independent of their estimated nitrate content.

Key words: Gastric cancer, Nitrate, Nitrite, Nitrosamine

Introduction

A human model of gastric carcinogenesis has been proposed, based on a multistage process in which dietary constituents act on the mucosa at various stages, leading from superficial gastritis to carcinoma, and N-nitroso compounds are suspected of playing an important role in this process [12]. Briefly, salt, salty foods and Helicobacter pylori infection may interfere as irritants to induce inflammation and atrophy of the mucosa. After the onset of atrophic gastritis, hypochlorhydria may be observed as well as increased nitrite concentrations in the stomach through the growth of bacteria able to reduce dietary nitrates to nitrites. Exogenous nitrites from diet or endogenous nitrites derived from nitrates could produce nitrosamines after nitrosation reaction with amines. These nitrosamines of endogenous origin, as well as those pre-formed in certain food products, may then induce precancerous lesions which could progress to carcinoma, Many antioxidants, such as vitamins C and E, could modify the synthesis of N-nitroso compounds. The occurrence of some stages of these processes has been confirmed in humans [20, 21]. The carcinogenicity of nitrosamines to the liver in animal models has been known since 1956 [24]. There is no firm proof of the carcinogenicity of nitrosamines in humans, but ecological studies suggest that nitrates (and consequently nitrites and nitrosamines) play a role in the aetiology of gastric cancer. Drinking water with high nitrate levels has been found in some areas with high incidence of gastric cancer, especially in China, Colombia and Hungary [1, 22]. In Japan, however, the incidence of this cancer is declining although consumption of foods treated with salt and containing nitrate remains important. On the other hand, metabolic investigations (nitrate excretion in urine, nitrate excretion in saliva, endogenous nitrosamine quantification and N-nitroso compounds in gastric juice) have shown inconsistent results and have not provided clear support for the 'N-nitroso compound' hypothesis [3, 9, 13, 14, 23, 29]. Numerous epidemiological studies have investigated the association between gastric cancer and usual diet but, to our knowledge, only a few of them have included estimates of N-nitroso compounds and their precursors [4, 8, 27]. Assessing individual exposure to nitrate, nitrite, and nitrosamine through diet is extremely complex, as the concentrations found in different food samples can vary considerably depending, for example, on how much fertilizer has been used, and the duration and condition of storage and cooking methods. The present case-control study was carried out in Marseille, a town located on the Mediterranean coast of France, an area where mortality rates from stomach cancer are quite low compared to other regions of France and southern Europe. During the 1980s, the annual age-standardized mortality rates among males in the Département of Marseille

(Bouches du Rhône) were of the order of 9–11 cases per 100,000 subjects per year. Comparable figures are 20–25 in the North of France and 34–45 in Northern Italy [28]. It was primarily designed to study in a French population the role of diet in gastric cancer risk, including the role of nitrite, nitrate and nitrosamine which are the object of this report.

Materials and methods

Materials and Methods are described in detail in a companion paper [11]. Briefly, from 1985 to 1988, all histologically confirmed incident cases of gastric adenocarcinoma, identified in the departments of gastroenterological surgery of eight major public and private centres for gastric surgery in Marseille, were considered for inclusion in the study. Controls were subjects undergoing functional re-education for trauma or injuries in two specialized medical centres, and were group matched to cases by sex and age distribution. Inclusion in the study was restricted to French citizens who had lived in France for at least 20 years. None of the eligible subjects refused to participate.

Interviews, conducted in hospital by a trained dietician, included questions on demographic characteristics, socio-economic status, occupation, medical history, occurrence of cancer among relatives, tobacco and alcohol consumption. Dietary patterns were assessed by means of a diet history questionnaire [26] which was expanded to include details on the main dietary sources of nitrate, nitrite and nitrosamine (i.e. different varieties of vegetables, smoked, cured and salted foods, beer, etc.) (see Appendix). For each food item, subjects were asked about their usual portion size and their average frequency of consumption during the previous year for controls or the year preceding the first symptoms of the disease for cases. Seasonal consumption was also taken into account and averaged out for the duration of the period of consumption.

Values for nitrite, nitrate and N-nitrosodimethylamine (NDMA) in foods were estimated by means of a composition table based on literature data [10]. For practical reasons, this table included only NDMA as a marker of nitrosamine, for which more analytical data on food were available. In order to calculate the total nitrate and nitrite intake, fresh vegetables were subdivided into three main groups according to their mean nitrate and nitrite content (see Appendix).

Odds ratios (ORs) were calculated as a measure of association between stomach cancer risk and dietary variables. Adjustment was made for total calorie intake (including calories from alcohol) using the method proposed by Willett & Stampfer [31]: residuals from the regression model with total calorie intake (as the independent variable) and absolute intake of food or food component (as the dependent variable), as well as total calorie intake (3 levels) were included as independent variables in the regression model fitted to calculate the ORs for a given dietary variable. For each dietary variable, residuals were categorized into tertiles defined by daily intake among controls. In addition all models included terms for sex, age ($\leqslant$55, 56 to 65, 66 to 75, $\geqslant$76 years) and occupation as proxy variables for socio-economic status (5 levels). Finally, adjusted ORs estimates for each residual, 95% confidence intervals (CI), chi-squares for linear trend (1 df; residuals being considered as continuous variables) were obtained by unconditional logistic regression [6].

Results

A total of 92 cases (59 men and 33 women) and 128 controls (74 men and 54 women) were interviewed. The distributions of cases and controls were similar for sex and age (means $\pm$ SD respectively: 66.6 $\pm$ 10.4 and 66.5 $\pm$ 9.8 years), as well as for height, weight, marital status, nationality and family history of stomach cancer.

Table 1 reports mean, median, 25th and 75th percentiles of daily intake of nitrate, nitrite, NDMA and 3 classes of vegetables according to their mean nitrate content for cases and controls. Average intake of NDMA was significantly higher for cases than for controls. Average intake of nitrate from vegetables and fruit as well as intake of vegetables with low- or high-nitrate content were significantly lower for cases than for controls. No significant differences in the intake of other items were found between cases and controls.

An increase in risk for gastric cancer was observed for high levels of intake of NDMA, with the ORs for the second and third tertiles equal to 4.13 (95% CI = 0.93 to 18.27) and 7.00 (95% CI = 1.85 to 26.46), respectively, Statistical analysis based on a continuous variable for NDMA intake (µg per day) confirmed this association and found a linearly increased risk of gastric cancer with increasing intake of NDMA (p = 0.04). There was no increase in risk for total nitrate intake nor for total nitrite intake (Table 2). A moderate decrease in risk was found with regard to intake of nitrate or nitrite derived from vegetables and fruit whereas an increased risk was observed with regard to nitrate or nitrite intake from other food sources, but none were statistically significant.

A reduced gastric cancer risk was found with increasing consumption of vegetables. The decreased risk was statistically significant for low-nitrate vegetables (OR_3 = 0.45, 95% CI = 0.22 to 0.92) and approached statistical significance for high-nitrate vegetables (OR_3 = 0.53, 95% CI = 0.26 to 1.09) (Table 3).

Table 1. Means, medians, 25th and 75th percentiles of daily intake of n-nitrosodimethylamine (NDMA), nitrate and nitrite (total intake and intake by food source) and intake of vegetables classified by nitrate content, for cancer cases and controls

	Cases				Controls			
	Mean ± SD	Percentile distribution			Mean ± SD	Percentile distribution		
		25%	Median	75%		25%	Median	75%
Total nitrate (mg)	143.20 ± 63.46	89.03	137.26	192.73	143.19 ± 50.76	112.12	145.96	181.90
Total nitrite (mg)	1.96 ± 0.54	1.61	1.98	2.26	1.94 ± 0.49	1.59	1.88	2.29
NDMA (μg)**	0.55 ± 0.87[d]	0.20	0.25	0.51	0.33 ± 0.50	0.19	0.23	0.29
Nitrate from vegetables and fruit	110.50 ± 60.91	58.08	100.62	150.65	114.07 ± 48.21	75.78	114.77	152.00
Nitrate from other foods	32.70 ± 15.84	24.87	30.45	34.50	29.12 ± 9.33	22.81	27.45	34.66
Nitrite from vegetables and fruit	0.99 ± 0.36	0.72	1.00	1.21	1.04 ± 0.32	0.86	1.07	1.25
Nitrite from other foods	0.97 ± 0.40	0.72	0.91	1.13	0.90 ± 0.37	0.63	0.85	1.08
Low-nitrate vegetables[a]**	33.84 ± 21.90	14.29	35.00	42.86	40.84 ± 21.27	28.57	42.86	57.14
Medium-nitrate vegetables[b]	165.40 ± 72.26	121.43	160.71	198.21	165.73 ± 59.66	128.57	160.71	200.00
High-nitrate vegetables[c]*	39.75 ± 28.43	17.15	35.71	57.14	47.09 ± 26.21	28.57	42.86	71.43

* $p < 0.05$; ** $p < 0.01$ for Wilcoxon sum-rank test
[a] Vegetables considered to have a low concentration of nitrate (i.e. mushrooms, peas, chicory, onions, tomatoes).
[b] Vegetables considered to have a medium concentration of nitrate (i.e. cucumber, egg-plant, courgettes, spinach, green beans, leeks, cabbage, carrots).
[c] Vegetables considered to have a high concentration of nitrate (i.e. Swiss chard, beetroot, lettuce, radishes).
[d] One extreme value excluded from the computation of the mean.

Table 2. Odds ratios (ORs)[a] for gastric cancer associated with exogenous NDMA and their precursors

	OR_1	OR_2 (95% CI)	OR_3 (95% CI)	p value for trend[b]
Total nitrate	1	0.49 (0.24–1.01)	0.76 (0.38–1.50)	0.96
Total nitrite	1	0.83 (0.41–1.67)	0.88 (0.44–1.79)	0.49
NDMA	1	4.13 (0.93–18.27)	7.00 (1.85–26.46)	0.04
Nitrate from vegetables and fruit	1	0.52 (0.26–1.07)	0.73 (0.37–1.45)	0.89
Nitrate from other foods	1	1.39 (0.66–2.91)	1.76 (0.88–3.54)	0.30
Nitrite from vegetables and fruit	1	0.74 (0.37–1.48)	0.77 (0.38–1.57)	0.36
Nitrite from other foods	1	1.47 (0.73–2.95)	1.15 (0.56–2.33)	0.99

[a] ORs were adjusted for age, sex, occupation and total calorie intake as indicated in the text.
[b] On continuous variables (absolute levels) as indicated in the text.

The RR for subjects in the higher tertile of intake of vitamin C compared to subjects in the lower tertile was 0.43 (95% CI: 0.20–0.94), indicating a substantial protection associated with high vitamin C intake. However, when we analysed the risk for nitrosamines in three separate strata of subjects with low, medium and high vitamin C intake, we found no meaningful differences which could suggest a biological interaction between intake of pre-formed nitrosamines and vitamin C. The risk for high intake of nitrosamines

Table 3. Odds ratios (ORs)[a] for gastric cancer associated with consumption of vegetables with low, medium and high nitrate content

	OR_1	OR_2 (95% CI)	OR_3 (95% CI)	*p* value for trend[b]
Low-nitrate-vegetables[c]	1	0.63 (0.32–1.24)	0.45 (0.22–0.92)	0.03
Medium-nitrate vegetables[d]	1	0.60 (0.29–1.23)	1.12 (0.57–2.20)	0.48
High-nitrate vegetables[e]	1	0.53 (0.27–1.05)	0.53 (0.26–1.09)	0.07

[a] ORs were adjusted for age, sex, occupation and total calorie intake as indicated in the text.
[b] On continuous variables (absolute levels) as indicated in the text.
[c] Vegetables considered to have a low concentration of nitrate (i.e. mushrooms, peas, chicory, onions, tomatoes).
[d] Vegetables considered to have a medium concentration of nitrate (i.e. cucumber, egg-plant, courgettes, spinach, green beans, leeks, cabbage, carrots).
[e] Vegetables considered to have a high concentration of nitrate (i.e. Swiss chard, beetroot, lettuce, radishes).

was apparently higher in the group with high vitamin C intake (OR: 10.41) than in the group with low vitamin C intake (OR: 4.72). This is paradoxically the contrary to what one would expect, and it may simply be due to random fluctuations owing to the small number of cases in each level of joint exposure to vitamin C and nitrosamines.

Discussion

In the present study we assess the risk of gastric cancer in relation to estimated dietary intake of nitrate, nitrite and NDMA. The most important feature revealed by this investigation is the increased risk associated with increasing intake of exogenous NDMA. As far as we know, only 2 studies published to date have estimated dietary exposure to nitrosamine. One did not detect any such relationship [27] while a recent study in Spain, using a similar table for nitroso compounds in foods, found similar results [17]. Two studies, in Italy [8] and Germany [5], observed no association between gastric cancer and nitrate. Our results did not support the hypothesis that total intake of nitrate and nitrite increases the risk of gastric cancer. On the basis of the results of experimental studies in animals, it has been postulated that antioxidant agents, vitamin C and polyphenolic compounds in particular, which are ingested together with nitrate and nitrite through vegetables, may inhibit nitrosation and endogenous formation of nitrosamine [2, 14]. This hypothesis is supported by our findings that only intake of nitrate or nitrite from dietary sources other than vegetables and fruit was associated with an increased risk for gastric cancer (although it was not statistically significant). This is consistent with the decreased risk observed for the intake of two out of the three classes of vegetables considered in our study. On the other hand, nitrate and nitrite have never been known to be cancer initiators. As they may be implicated in gastric carcinogenesis as precursors of endogenously formed nitrosamines, we cannot directly transpose the results concerning these compounds. However, it was not possible to assay endogenous nitrosation from ingested nitrate and nitrite in the present survey.

Regarding the combined effects of intakes of vitamin C and pre-formed nitrosamines, we found no evidence of a statistical interaction between the two factors. However, the statistical power to detect such an interaction was low due to the limited sample size.

Our data did not allow us to examine the role of smoked, cured and salted fish and meat which were very rarely consumed in the population under study (less than two percent consumers). These food items, however, were accounted for in the total computation of nitrosamines and their precursors. In some eastern countries such as China and Japan, salted, dried and smoked fish, and fermented and pickled vegetables, which are products with high nitrosamine concentrations, are frequently consumed and have been linked to gastric cancer [18, 19, 30, 33]. In two Mediterranean countries, Italy and Spain, an increase in the risk of gastric cancer was associated with consumption of dried and preserved fish [7, 16] although the attributable risk for this type of exposure is probably very low in Western societies.

This study examines the risk for gastric cancer in relation to recent dietary habits (one year preceding the first symptoms or interview), assuming that current diet adequately reflects past diet [15]. However, this is unlikely to be representative of diet in childhood and adolescence which, it has been suggested, may be particularly relevant in the etiology of gastric cancer [25]. On the other hand, many epidemiological studies have indicated that diet

in adulthood is also likely to be involved in the aetiology of gastric cancer. In our study, NDMA could be a marker of overall intake of foods rich in nitroso compounds and poor in protective factors, and may therefore contribute to different stages of the carcinogenic process.

Analysis of the exposure to nitrite-nitrate-nitrosamine in food is particularly complex. Many N-nitroso compounds have been detected in food products but the best known and the most widely measured is N-nitrosodimethylamine (NDMA). For this reason, in the present study, only dietary exposure to NDMA was assessed although it may not be representative of the whole group of preformed nitrosamines in food. Nitrate and nitrite concentrations in food depend partly on environmental and external factors and can vary considerably for the same food product. In particular, as the amounts in vegetables depend on crop conditions, part of the plant used, storage and cooking methods, it is extremely difficult to create a composition table [10]. The nitrate and nitrite content of drinking water varies considerably from one site to another, depending on industrial pollution, local use of fertilizers and geochemical conditions [32]. In the urban area of Marseille, drinking water comes from the river Verdon in Provence which has a very low concentration of nitrate and nitrite (1.5 and 0.005 mg/litre respectively). In the present study it was not possible to take this factor into account due to the lack of information at the individual level.

However, the findings presented here are consistent with the biological hypothesis and provide support for a association between nitrosamine and gastric cancer.

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Appendix: Average concentrations of nitrite, nitrate and N-nitrosodimethylamine (NDMA in various foods used to estimate individual intake in this study

Foods	Nitrite (mg/kg)	Nitrate (mg/kg)	NDMA (μg/kg)
Dairy products			
Whole milk, half-fat milk skim milk	0	0.5	0.51
Yoghurt	0	0.5	0.01
Cream cheese (10% & 40%	0	0.5	0.01
Hard cheese	1.0	17.0	0.45
Soft cheese	0.7	16.0	
Meat and eggs			
Red meat	1.0	10.0	0
Horse meat	1.0	10.0	0
Poultry	1.0	10.0	0.11
Offal	1.0	10.0	0
Ham	15.8	156.6	0.40
Cured meat (sausages, bacon)	12.6	136.0	2.15
Smoked meat	12.0	139.3	0.35
Preserved meat	3.8	81.0	0.35
Eggs	1.0	10.0	0
Fish			
Fresh fish	1.0	11.8	0.22
Smoked fish	9.0	10.3	25.9
Shell fish	1.0	8.0	–
Tinned fish	–	–	0.48
Flour products			
White bread, wholemeal bread	1.3	25.0	0
Crispbread	1.3	25.0	0
Wholemeal crisp-bread	0	0	0
Wheat flour (78%)	1.2	8.5	0
Sandwich loaf	1.3	25.0	0
Cakes[a]	1.3	25.0	0
Pasta, rice	1.3	25.0	0
Bran	–	–	–
Sugar			
Sugar, chocolate and sweets	0	0	0.34
Jam	–	–	0
Fat			
Butter and cream (30%)	0	0	0
Oil (olive, peanut and sunflower	0	0	0
Fruit			
Fresh fruit	0	20.0	0
Olives	0	20.0	0
Nuts and dried fruit	–	–	–

Appendix (continued)

Foods	Nitrite (mg/kg)	Nitrate (mg/kg)	NDMA (μg/kg)
Vegetables			
Low-nitrate[b]	0.6	20.9	0.41
Medium-nitrate[c]	4.7	207.0	0.41
High-nitrate[d]	3.8	2026.5	0.41
Dried vegetables	–	13.0	–
Lettuce	6.8	1362.8	0
Tomatoes	0.3	30.8	0
Carrots	1.2	176.2	0
Beetroot	2.2	2136.2	0
Radishes	4.8	2576.8	0
Cucumber	5.4	156.5	0
Chicory	0.7	32.9	0
Green beans	12.6	150.4	0
Courgettes	–	90.0	0
Egg plant	–	179.0	0
Onion	0.3	17.0	0
Leeks	6.6	178.5	0
Swiss chard	1.3	2030.0	0
Spinach	7.7	442.6	0
Peas	0.7	10.1	0
Cabbage[e]	2.0	152.1	0
Mushrooms	0.9	13.5	0
Potatoes[g]	1.1	142.2	0
Beverages			
Beer	0	17.0	4.4[f]
Cider, wine (10°), fortified wine and spirits	–	–	0
Fruit juices	–	–	0
Fizzy drinks	–	–	0
Coffee, tea and decaffeinated coffee	–	–	0
Spirits	–	–	1.8

–: Unknown value.
[a] This group includes: brioche, croissants, tarts, sponge cakes, cream cakes, biscuits.
[b] Vegetables considered to have a low concentration of nitrate (i.e. mushrooms, peas, chicory, onions, tomatoes).
[c] Vegetables considered to have a medium concentration of nitrate (i.e. cucumber, egg-plant, courgettes, spinach, green beans, leeks, cabbage, carrots).
[d] Vegetables considered to have a high concentration of nitrate (i.e. Swiss chard, beetroot, lettuce, radishes).
[e] This group includes: cauliflower, red kale, cabbage, Brussels sprouts
[g] Potatoes were included in the total intake of nitrite and nitrate, but were not included in the 3 classes of vegetables.
[f] Value commonly found during the 1970s. Current mean values in France are around 0.28.

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